

Complete Summary

GUIDELINE TITLE

The investigation and treatment of couples with recurrent miscarriage.

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2003 May. 13 p. (Guideline; no. 17). [88 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Recurrent miscarriage

GUIDELINE CATEGORY

Evaluation
 Management
 Risk Assessment
 Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Medical Genetics
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To review the literature and provide guidance on the investigation and treatment of couples with recurrent miscarriage

TARGET POPULATION

Couples with recurrent miscarriage

INTERVENTIONS AND PRACTICES CONSIDERED

1. Peripheral blood karyotyping
2. Referral to a clinical geneticist
3. Cytogenetic analysis of the products of conception
4. Cervical cerclage (not recommended routinely because of risk of stimulating uterine contractions)
5. Transvaginal ultrasound assessment of the cervix
6. Screening for primary antiphospholipid syndrome (APS)
7. Aspirin plus heparin therapy for antiphospholipid antibodies (aPL)
8. Screening for and treatment of bacterial vaginosis
9. Supportive care for women with unexplained recurrent miscarriage

The following interventions were considered but not recommended: Progesterone supplementation, human chorionic gonadotrophin supplementation, prepregnancy suppression of high luteinising hormone (LH), screening for thyroid antibodies, steroid treatment, immunotherapy; screening for TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, and herpes simplex virus).

MAJOR OUTCOMES CONSIDERED

- Miscarriage rate
- Incidence of abnormal parental karyotype
- Healthy live birth rate
- Prevalence of foetal chromosomal abnormality
- Perinatal survival from ultrasound-indicated cervical cerclage
- Risk of pregnancy complications and side effects from treatments

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Cochrane Library and Cochrane Register of Controlled Trials were searched for relevant randomised controlled trials, systematic reviews, and meta-analyses. A search of Medline from 1966 to 2002 was also carried out. The date of the last search was February 2002. In addition, relevant conference proceedings and abstracts were searched.

The databases were searched using the relevant Medical Subject Heading (MeSH) terms including all sub-headings and this was combined with a keyword search using: human; female; pregnancy; abortion; miscarriage; habitual; recurrent; randomised controlled trials; meta-analysis.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

I a: Evidence obtained from meta-analysis of randomised controlled trials

I b: Evidence obtained from at least one randomised controlled trial

II a: Evidence obtained from at least one well-designed controlled study without randomisation

II b: Evidence obtained from at least one other type of well-designed quasi-experimental study

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

None stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The recommendations were graded according to the level of evidence upon which they were based.

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

Grade C - Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following discussion in the Guidelines and Audit Committee, each green-top guideline is formally peer reviewed. At the same time the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) website for further peer discussion before final publication.

The names of author(s) and nominated peer reviewers are included in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Levels of evidence (I a-I V) and grading of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Investigations and Treatments

Genetic Factors

C - All couples with a history of recurrent miscarriage should have peripheral blood karyotyping performed. The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist.

C - In all couples with a history of recurrent miscarriage cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.

Cytogenetic testing is an expensive tool and may be reserved for patients who have undergone treatment in the index pregnancy or have been participants in a research trial; for them, karyotyping the products of conception provides useful information for counselling and future management.

Cervical Weakness

B - Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should only be considered in women who are likely to benefit.

Transvaginal ultrasound assessment of the cervix during pregnancy may be useful in predicting preterm birth in some cases of suspected cervical weakness. [Evidence level Ib]

Endocrine Factors

A - There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage.

Exogenous progesterone supplementation should only be used in the context of randomised controlled trials. [Evidence level Ia]

A - There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin (hCG) in pregnancy to prevent miscarriage.

HCG supplementation in early pregnancy should only be used in the context of randomised controlled trials. [Evidence level Ib]

A - Prepregnancy suppression of high luteinising hormone (LH) concentration among ovulatory women with recurrent miscarriage and polycystic ovaries who hypersecrete LH does not improve the live birth rate.

B - Polycystic ovary morphology itself does not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.

A - There is insufficient evidence to assess the effect of hyperprolactinaemia as a risk factor for recurrent miscarriage.

Immune Factors

Antithyroid Antibodies

B - Routine screening for thyroid antibodies in women with recurrent miscarriage is not recommended.

Antiphospholipid Syndrome (APS)

C - To diagnose APS it is mandatory that the patient should have two positive tests at least six weeks apart for either lupus anticoagulant or anticardiolipin (aCL) antibodies of immunoglobulin G (IgG) and/or IgM class present in medium or high titre.

A - Currently there is no reliable evidence to show that steroids improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies (aPL) when compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity.

A - In women with a history of recurrent miscarriage and aPL, future live birth rate is significantly improved when a combination therapy of aspirin plus heparin is prescribed.

B - Pregnancies associated with aPL treated with aspirin and heparin remain at high risk of complications during all three trimesters.

Although aspirin plus heparin treatment substantially improves the live birth rate of women with recurrent miscarriage associated with aPL, these pregnancies remain at high risk of complications during the three trimesters including repeated miscarriage, pre-eclampsia, fetal growth restriction, and preterm birth, necessitating careful antenatal surveillance. [Evidence level III]

Alloimmune Factors

A - Immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes, and intravenous immunoglobulin (IVIG), in

women with previous unexplained recurrent miscarriage does not improve the live birth rate.

The use of immunotherapy should no longer be offered to women with unexplained recurrent miscarriage and routine tests for human leukocyte antigen (HLA) type and anti-paternal cytotoxic antibody should be abandoned. [Evidence level Ia]

The USA Food and Drug Administration has recently issued a statement to clinicians that administration of such cells or cellular products in humans can only be performed by a licensed clinical researcher holding a currently approved Investigational New Drug application.

Infective Agents

C - TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, and herpes simplex virus) screening is unhelpful in the investigation of recurrent miscarriage.

A - Screening for and treatment of bacterial vaginosis in early pregnancy among high-risk women with a previous history of second-trimester miscarriage or spontaneous preterm labour may reduce the risk of recurrent late loss and preterm birth.

Inherited Thrombophilic Defects

In the absence of a randomised trial, the poor pregnancy outcome associated with factor V Leiden (FVL) mutation, coupled with the maternal risks during pregnancy, may justify routine screening for FVL and offering thromboprophylaxis for those with FVL mutation and evidence of placental thrombosis.

Unexplained Recurrent Miscarriage

C - Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.

Data suggest that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted. Further, clinical evaluation of future treatments for recurrent miscarriage should only be performed in the context of randomised trials that are suitably matched and corrected to exclude fetal chromosomal aberrations. [Evidence level IV]

Definitions:

Grading of Recommendations

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

Grade C - Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

Levels of Evidence

I a: Evidence obtained from meta-analysis of randomised controlled trials

I b: Evidence obtained from at least one randomised controlled trial

II a: Evidence obtained from at least one well-designed controlled study without randomisation

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IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate evaluation and management of couples with recurrent early pregnancy loss to increase the outcome for a successful live birth

POTENTIAL HARMS

- Transabdominal cerclage may be associated with a higher risk of serious operative complications

- Osteopenia and vertebral bone fracture are the major concern of long-term heparin therapy. Two prospective studies have shown that the loss in bone mineral density at the lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs physiologically during pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Clinical guidelines are "systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions." Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: Guidance for the Development of Royal College of Obstetricians & Gynaecologists (RCOG) Green-top Guidelines.
- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2003 May. 13 p. (Guideline; no. 17). [88 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 May

GUIDELINE DEVELOPER(S)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

SOURCE(S) OF FUNDING

Royal College of Obstetricians and Gynaecologists

GUIDELINE COMMITTEE

Guidelines and Audit Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor Deirdre J Murphy, MRCOG (Chair); Lizzy Dijeh (Secretary); Ms Toni Belfield, Consumers' Representative; Professor P R Braude, FRCOG, Chairman, Scientific Advisory Committee; Mrs C Dhillon, Head of Clinical Governance and Standards Dept.; Dr Martin Dougherty, A. Director NCC-WCH; Miss L M M Duley, FRCOG, Chairman, Patient Information Subgroup; Mr Alan S Evans, FRCOG; Dr Mehmet R Gazvani, MRCOG; Dr Rhona G Hughes, FRCOG; Mr Anthony J Kelly MRCOG; Dr Gwyneth Lewis, FRCOG, Department of Health; Dr Mary A C Macintosh, MRCOG, CEMACH; Dr Tahir A Mahmood, FRCOG; Mrs Caroline E Overton, MRCOG, Reproductive medicine; Dr David Parkin, FRCOG; Oncology; Ms Wendy Riches, NICE; Mr Mark C Slack, MRCOG, Urogynaecology; Mr Stephen A Walkinshaw, FRCOG, Maternal and Fetal Medicine; Dr Eleni Mavrides, Trainees Representative

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Guideline authors are required to complete a "declaration of interests" form.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

Print copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Bookshop, 27 Sussex Place, Regent's Park, London NW1 4RG; Telephone: +44 020 7772 6276; Fax, +44 020 7772 5991; e-mail: bookshop@rcog.org.uk. A listing and order form are available from the [RCOG Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance for the development of RCOG green-top guidelines. Clinical Governance Advice No 1. 2000 Jan. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).
- Searching for evidence. Clinical Governance Advice No 3. 2001 Oct. Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#).

PATIENT RESOURCES

The following is available:

- Couples with recurrent miscarriage: what the RCOG guideline means for you. Royal College of Obstetricians and Gynaecologists, 2004 Aug. 8 p. Electronic copies: Available from the [Royal College of Obstetricians and Gynaecologists Web site](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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